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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/721,763	11/26/2003	Eiji Mori	081356-0207	6356

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

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02/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,763	MORI ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *108-112* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *copy of Table 1*.

DETAILED ACTION

Response to Amendment

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims.

Claims 108-112 are no longer rejected under 35 USC 112, first paragraph, in view of the amendment to the claims. Note that claims 63-104 remain rejected.

Specification

The disclosure remains objected to because of the following informalities: Tables 1-2 beginning on page 56 shows no information because all the symbols for cross-reactivity are identical. Tables 3-4 on pages 61-63 do not use the symbols of the legend and, therefore, provide no information. Appropriate correction is required.

Applicants state that the symbols in Tables 1-4 are correct in the specification. This is true of the original specification filed 11/26/03; however, the substitute specification filed 6/7/04 shows all the +'s and -'s replaced by □'s. The legends of Tables 1-2 also have □'s and legend of Table 4 has "□" replacing a ":". See attached Table 1, for example.

Claim Objections

Claim 108 is objected to because of the following informalities: Because of the amendment to the claim in section (i), there is no longer an "or" between alternative immunizing agents. That is, there is now only a comma between the only two alternatives:"TRAIL-R2 or an extracellular fragment thereof, cells expressing the TRAIL-R2 or an extracellular fragment thereof". Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-104 as amended remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monoclonal antibody 0304 or 0322 or a functional fragment of either monoclonal antibody which is monomeric and free of any polymeric forms or for a therapeutic agent against tumors comprising said monoclonal antibody or functional fragment thereof as an active agent, does not reasonably provide enablement for other monoclonal antibodies or functional fragments thereof which are only present in monomeric form. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the relevant reasons set forth in the previous Office action.

Applicants argue that the inventors discovered "a distinct subpopulation of monoclonal antibodies, which the inventors discovered to be routinely obtainable, that need not polymerize with one another or act with some other exogenous factor(s) in order to induce cell death. For this reason, the inventors said: "we have … succeed[ed] for the first time in the world in producing a novel monoclonal antibody" that has "no side effects of inducing cytotoxicity against" normal hepatocytes, a problem with conventional anti-TRAIL-R2 antibodies...." The argument has been fully considered, but is not persuasive. Even though the specification uses methods to produce antibodies with the claimed properties which were known in the art, the combination of different methods was not routine for antibody production/isolation. (Note that the method of producing the claimed antibody, claims 108-112, are enabled.) Nor did all antibodies produced by the combined methods have the required properties. As stated in the previous Office action (paragraph bridging pages 3-4), monoclonal antibodies 0304 and 0322 did, but antibody H-48-2 did not. Further, prior art antibody TRA-8 which appeared to have the required properties was shown by Inventor Dr. Motoki (declaration filed 4/2/08) not to possess apoptosis-inducing activity in monomeric form. Other prior art antibodies were investigated and, as stated in the previous Office action (end of first full paragraph on p. 4), "Dr. Motoki's final conclusion is as follows (paragraph 9 of the declaration): "In summary, I conclude that none of the prior-art antibodies can induce apoptosis in monomeric form. We found that the prior-art antibodies were able to induce apoptosis only when they formed polymeric antibody aggregates." This supports the conclusion that it was unpredictable if the monomeric form of an antibody would meet the limitations required in the claims

Applicants argue that the inventors discovered a "subclass of monomeric antibodies" having the required properties, and that the specification "teaches the skilled person how to access, in routine fashion, the previously unrecognized subpopulation of monomerically-active, monoclonal antibodies...." The argument has been fully considered, but is not persuasive. That the method of producing the claimed antibody is not obvious and the subclass or monomeric antibodies was previous undiscovered supports nonenablement for the full scope of the claims. Also, as stated in the previous Office action (middle of p. 5):

> Even though the relative skill of those in the art is high, fractionation of antibodies to separate monomeric and polymeric forms is not routine in the apoptosis or TRAIL receptor art. The art provides no predictability about the ability of a monomeric fraction of any give antibody to meet the limitations required in the claims. The specification provides working examples of only three monoclonal anti-TRAIL-R2 antibodies that induced apoptosis upon binding to TRAIL-R2, and of these, only two had monomeric fractions which retained the ability to induce apoptosis in the absence of cross-linking (or exogenous factors). The claims have breadth as currently written because they are drawn to a genus of antibodies. While the specification provides guidance by the inventors about assays that may be used to screen antibodies, the results are completely unpredictable--even at the point one has isolated a monoclonal antibody which can induce apoptosis upon binding to TRAIL-R2--because monomers of that antibody may or may not also induce apoptosis upon binding without exogenous factors. For these reasons and those discussed above, it would require undue experimentation to make and/or use the invention.

Applicants argue that there is no reasonable basis for questioning whether further monoclonal antibodies that meet the claim limitations can be made based on the instant specification. Neither the effort nor degree of predictability is "undue", "but instead is endemic or routine to the field." The argument has been fully considered, but is not persuasive. It may be that further antibodies can be made that meet the claim limitations, but the question is whether it would require undue experimentation to make them--whether the claimed invention is commensurate in scope with enablement. For the reasons discussed in the previous Office action and above, including state of the prior art, paucity of working examples, breadth of the claims, unpredictability concerning the functional properties of monoclonal antibodies as they relate to polymeric *vs.* monomeric forms, it is maintained that practicing the invention commensurate in scope with the claims would require undue experimentation.

Allowable Subject Matter

Claims 108-112 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.
/Claire Kaufman/
Patent Examiner, Art Unit 1646
January 29, 2009

Lorraine Spector, Ph.D.

/Lorraine Spector/

Primary Examiner, Art Unit 1647